Biotechnology Industry Organization
1225 Eye Street NW, Suite 400
Washington, DC 20005

May 11, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20857

Re: Docket No. 2004N-0087, Federal Register March 3, 2004 (Volume 69, Number 42, Page 9982) "Generic Drug Issues; Request for Comments" – Comments on Bioavailability and Bioequivalence Standards.

Dear Sir or Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products. We are writing in response to the request by the Food and Drug Administration (FDA) for comments on certain provisions in Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA). Our comments concern the new statutory provisions concerning bioavailability and bioequivalence standards for the approval of generic drug products under section 505(j) of the Food, Drug, and Cosmetic Act (FDCA).

Prior to the enactment of MMA, the term bioavailability was defined under FDCA to mean "the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action" (21 USC 355(j)(8)). Bioequivalence, in turn, was also defined in terms of the "rate and extent of absorption" of a test and a reference drug.

Under MMA, an alternative definition of bioavailability and bioequivalence has been added with the explicit purpose of addressing a limited number of drug products that are

not intended to be absorbed into the blood stream and for which systemic measures of absorption are not meaningful.[1]. Thus, FDCA, as amended by MMA, now provides:

> For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action (505(j)(8)(A)(ii)).

Thus for non-systemic drug products, such as topical and ophthalmic drugs, MMA allows for a determination of bioavailability based solely on the rate and extent to which the active ingredient becomes available at the site of drug action. No demonstration or evaluation of systemic absorption is required.

Prior to MMA, FDA interpreted section 505(j) of FDCA to allow for a range of methods by which bioavailability or bioequivalence could be determined. The methods established by FDA included methods that relied on non-systemic measures of bioavailability and bioequivalence. FDA's regulations prior to MMA generally have been upheld by the courts, and, in fact, FDA has approved numerous drug products under section 505(j) that are not intended for systemic absorption.

In that light, we understand the new statutory language of MMA to accomplish two limited goals. First, it documents FDA's existing regulations in 21 CFR 320.24. Second, and importantly, the provision requires the Secretary of Health and Human Services (the Secretary) to establish "scientifically valid" measures to determine bioavailability and bioequivalence of drug products not intended for systemic absorption. This requirement for scientific validity is not contained in FDA's current general bioavailability/ bioequivalence regulations. While these current regulations allow for a demonstration of bioavailability and bioequivalence based on different types of evidence, the new statutory provisions of MMA require the Secretary (and, by delegation of authority, FDA) to establish drug-specific methodologies that have been fully validated.

Therefore, in response to FDA's request for comments, BIO strongly recommends that FDA consider the process it will use to establish such standards and to involve all interested persons, including innovators, in the development of standards. We also ask that FDA confirm the limited scope of the new, alternative standard – as applicable to

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[1] As explained by one of the original sponsors of this provision: "Under the current statute, the primary method by which the FDA determines whether a generic is equivalent to a brand drug ("bioequivalence") is by measuring the rate and absorption of the drug into the bloodstream. For certain drugs which are not absorbed into the bloodstream, such as topicals and inhalers, the FDA uses different tests to determine bioequivalence, which are defined in their regulations. . . . *Gregg-Schumer would clarify that the FDA does have the authority to establish separate tests for determining the bioequivalence of drugs which are not absorbed into the bloodstream - as long as those tests are scientifically valid and meet rigorous standards.*" Press Release by Senator Charles E. Schumer (D-N.Y.), *Schumer Generic Drug Legislation Passes Full Senate* (June 19, 2003) (emphasis added).

topical, ophthalmic, and other products not absorbed into the systemic blood stream – and define the products or categories of products for which these provisions would not apply.

We thank you for inviting comments on this important topic, and look forward to future collaborations with FDA on this matter.

Sincerely,

Sara Radcliffe
Director
Science Policy and Bioethics